CHAPTER 33

Mild Cognitive Impairment: Pivotal Cingulate Damage in Amnestic and Dysexecutive Subgroups

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Chapter contents

Advancing age is associated with a wide variation of cognitive functioning. While some individuals experience little to no change in their thinking abilities, others develop significant cognitive decline and dementia. Cognitive impairment in the absence of dementia in individuals over the age of 65 is common. Several large epidemiological studies suggest that cognitive impairment without dementia is two to five times more common than dementia and is present in 11-27% of the population (Hanninen *et al.*, 1996; Graham *et al.*, 1997; Schroder *et al.*, 1998; Di Carlo *et al.*, 2000; Unverzagt *et al.*, 2001; Lopez *et al.*, 2003). The prevalence of cognitive impairment increases with age. Unverzagt *et al.* (2001) reported that 29% of individuals between 65 and 74 years of age and as many as 55% of individuals over the age of 84, exhibited symptoms of cognitive impairment without dementia. Neurodegenerative disorders are proposed to account for the majority of cognitive decline in later adulthood, but cognitive decline can also occur in other conditions, such as depression, medical illness, and to some degree, aging (Ritchie *et al.*, 2001; Unverzagt *et al.*, 2001).

'Mild cognitive impairment' (MCI) is a clinical term that refers to a decline in cognition in older adults that does not meet the criteria for dementia. The term MCI was popularized by Petersen *et al.* (1999) who argued that MCI is a transitional stage between healthy aging and dementia (Petersen *et al.*, 2001). Although some groups view MCI as an early stage of Alzheimer disease (AD; Morris *et al.*, 2001; Lambon Ralph *et al.*, 2003), several studies report that some individuals diagnosed with MCI do not progress to dementia and some may revert to normal (Collie & Maruff, 2000; Ritchie *et al.*, 2001; Larrieu *et al.*, 2002). As MCI cases can be either stable or AD-converting, it is important to define markers for each and the course of conversion so that ensuing AD can be predicted.

Of particular importance to the present consideration is the fact that posterior and to some extent midcingulate cortex (MCC) have been implicated as the first site of reduced cerebral blood flow, in MCI. Imaging of early AD shows a reduction in regional cerebral blood flow (rCBF) and glucose metabolism in posterior cingulate cortex (PCC; Salmon *et al.*, 1994; Jagust *et al.*, 1995; Minoshima *et al.*, 1997), and hypometabolism in this region correlates with performance on a test of constructional praxis (Nobili *et al.*, 2005). Hypometabolism has also been shown in PCC in amnestic MCI (Nestor *et al.* 2003) and, although not all MCI subjects convert to AD, reductions in PCC metabolism may help predict which MCI patients will convert (Kantarci *et al.*, 2000; Chetelat *et al.*, 2003). Huang *et al.* (2002) noted that a reduction in PCC rCBF occurred up to 2 years before the AD diagnosis, and Johnson *et al.* (1998) found that rCBF values from the cingulate gyrus, hippocampus-amygdala and thalamus identified about 80% of MCI patients who converted to AD. Thus, conversion from MCI to AD may critically depend on events in PCC.

Drzezga *et al.* (2003) observed glucose hypometabolism in PCC and medial parietal cortex in MCI, and patients that converted to AD 1 year later had an additional glucose hypometabolic site in prefrontal cortex. They suggested that prefrontal involvement marks the transition from MCI to AD. Nobili *et al.* (2005) correlated rCBF with performance on a number of behavioral tasks and observed a high correlation between reduced perfusion and constructional apraxia in PCC and precuneal cortex. Thus, the links between PCC and prefrontal damage may be of particular interest to determining the mechanisms of the MCI-to-AD conversion.

In view of the relevance of prefrontal cortex to conversion from MCI to AD, it is surprising that few neuropathological changes have been observed in neocortex, including prefrontal cortex, with the exception of amyloid-β peptide (Aβ) deposition in diffuse plaques (Price, 1991; Morris *et al.*, 1996, 2001). Frontal expression of α-synuclein, myelin basic protein, ubiquitin, synapse markers, Aβ40, Aβ42, and paired helical fibrils (PHF-tau) show no difference between MCI and healthy elderly controls (Wang *et al.* 2001, 2004). A lack of frontal pathology in clinically characterized MCI patients may reflect a sampling bias with the general focus on amnestic MCI and memory networks, rather than impairments of judgment and executive function mediated by the frontal lobe.

Goals of This Chapter

MCI is an important focus of cognitive aging and, as a prodromal form of AD, an important intermediary in the transition to dementia. In view of the pivotal role of PCC in MCI and its conversion to AD, this chapter considers the characteristics of MCI with a particular focus on the cingulate gyrus in amnestic MCI and a variant of MCI with frontal damage and dysexecutive characteristics. As it is a very early cortical neuropathology, our MCI case that reached postmortem analysis provides a unique context for evaluating an early stage of cingulate neurodegeneration and linking the progressive deposition of markers in the cingulate gyrus and frontal lobe. The specific chapter goals include:

1. Review the history of the MCI concept and definition of the clinical characteristics, and the outcomes of amnestic MCI.
2. Co-register imaging findings to a postmortem case to precisely localize cingulate damage.
3. Evaluate cingulate gyrus and frontal lobe neuropathology in the case of dysexecutive MCI with antibodies

to tau, Aβ42 and Aβ40, and link their laminar deposition to neurodegeneration.

4 Provide new findings of an antibody to an early tau conformation that is unique to AD (MC1), to identify secondary sites of pathology that alert to progressive damage in the cingulate gyrus.

5 Evaluate cell cycle protein expression with proliferating cell nuclear antigen (PCNA) to determine if early pathological events can be detected in cingulate neurons that re-entered the cell cycle.

6 Describe the primary focus of dPCC/MCC damage and its progression both in terms of postmortem pathology and longitudinal imaging studies.

7 Consider the hypothesis that, although MCI always appears to first involve a part of area 23d in dPCC, there are two pathways for AD progression; one that evolves caudally in amnestic MCI and another that evolves rostrally in dysexecutive MCI.

History of the MCI Concept

The concept of MCI developed from the observation that some older adults experience a decline in cognition with age. As early as the late 19th century, George Humphry (1889) noticed a range of memory and intellectual functioning in a sample of almost 900 adults over the age of 80. Additional studies about cognitive variability with age continued through the early 20th century with work by G. Stanley Hall, Lillien Martin, Catharine Cox Miles, and Walter R. Miles (Hirshbein, 2002). An interest in studying changes in cognition with age gained momentum in the late 1950s and 1960s. Kral (1958a,b, 1962) differentiated 'benign' and 'malignant' senescent forgetfulness. He identified individuals who had poor recall of event details but could remember the general event and noted that they were aware of the difficulty and could usually eventually recall the event. After 4 years, only one of the 20 subjects with the benign form declined, whereas all with the malignant form declined (Kral, 1978). In contrast, 'malignant' senescent forgetfulness was characterized as poor memory for details and events and a lack of awareness. Also at this time, Roth *et al.* (1966, 1967) proposed that accumulation of neuritic plaques was related to cognitive decline and dementia.

Following these early studies, there was an explosion of new clinical terms. (Table 33.1). There was a trend in the 1980s to attribute a slight decline in cognition to a very early stage of dementia such as 'questionable dementia' (Hughes *et al.*, 1982), 'minimal dementia' (Roth *et al.*, 1986), and 'limited dementia' (Gurland *et al.*, 1982). In 1986, the National Institute of Mental Health proposed the term 'age-associated memory impairment' to refer to individuals who scored greater than one standard deviation below young adults on tests of memory (Crook *et al.*, 1986). This was the first attempt to operationalize the definition. 'Late-life forgetfulness' was proposed in 1989 to classify individuals who scored 1.5 to 2 standard deviations below age-matched norms on memory tests (Blackford, 1989). Flicker *et al.* (1991) identified a group of individuals with MCI as defined by a score of 3 on the Global Deterioration Scale. Most recently, the term MCI has been widely applied to label individuals who exhibit memory impairment in the absence of dementia or functional impairment (Petersen *et al.*, 1999, 2001).

TABLE 33.1 Terms for Mild Cognitive Impairment

Year	Term	Authors
1962	Benign senescent forgetfulness	Kral (1962)
1986		Crook ***et al.*** (1986)
1992	Late life forgetfulness	Blackford (1989)
1992	Mild cognitive impairment (ICD-10)	Zaudig (1992)
1993	Mild cognitive disorder (ICD-10)	WHO (1993)
1994	Age-Associated cognitive decline (AACD)	Levy (1994)
1994	Mild cognitive decline (DSM-IV)	APA (1994)
1997	Cognitive impairment no dementia (CIND)	Graham ***et al.*** (1997)
1998	Age-related cognitive decline (ARCD)	APA (1998)
1999	Mild cognitive impairment (MCI)	Petersen ***et al.*** (1999)

By definition, all of the classifications discussed above focused on a decline in memory and not other cognitive domains. In contrast, 'age-associated cognitive decline' (Levy, 1994), 'age-related cognitive decline' (APA, 1994), and 'cognitive impairment no dementia' (CIND) (Graham *et al.*, 1997) were developed to classify individuals who exhibit impairment on *any* cognitive domain, including memory. Despite the existence of numerous terms for cognitive impairment in elderly individuals, MCI and memory decline has become the focus of most studies of cognitive impairment in the absence of dementia in elderly individuals.

Clinical Characteristics of MCI

The majority of MCI research focuses on the amnestic subgroup, which is characterized by a relatively selective decline in memory function. However, it is becoming increasingly recognized that MCI is a clinically heterogeneous syndrome, and subgroups have been proposed. Individuals with amnestic MCI have mild difficulties recalling recent events or details of events.

These relatively minor memory difficulties generally do not interfere with basic day-to-day functioning, but it may take longer to complete more difficult tasks. The individuals may or may not have insight into these difficulties. On objective measure of episodic memory such as remembering word lists, stories, or pictures, amnestic MCI subjects commonly perform below the norm for their age (Petersen *et al*., 1999; Collie and Maruff 2000). They also commonly have lower-than-expected scores on tests of frontal-executive function, language, visuospatial skills, and/or praxis (Flicker *et al*., 1991; Hanninen *et al*., 1997), but the impairment in non-memory domains are not severe enough to interfere with daily activities or meet the criteria for dementia. The general clinical criteria used for MCI are in Table 33.2.

Non-memory presentations of MCI have also been proposed (Petersen *et al*., 2001; Lambon *et al*., 2003; Mapstone *et al*., 2003; Johnson *et al*., 2004), but less is known about the clinical characteristics and outcomes. MCI has been subdivided into impairment in a single cognitive domain (e.g., memory, executive, language, visuospatial) or a combination of mild impairments across several domains (i.e., MCI multiple domains; Lopez *et al*., 2003; Petersen, 2004; Table 33.2). Mapstone *et al*., (2003) described a visual variant of MCI who had selective impairment in visuospatial function and a preservation of memory. We describe a frontal-executive presentation of MCI below.

Differential Diagnosis of MCI

The variable clinical presentation of MCI suggests, there is a considerable variability in the underlying etiology. While the majority of research has focused on amnestic MCI and risk for AD, cognitive impairment in the absence of dementia can also occur in other neurodegenerative disorders (e.g., frontotemporal dementia, Huntington disease, major depression, schizophrenia). It is not surprising that most neurodegenerative disorders have a preclinical stage, as they often begin insidiously and progress gradually. Future studies will need to determine how the MCI stages of different neurodegenerative disorders overlap or differ.

A MCI stage of vascular dementia is a commonly studied variant. The term 'vascular cognitive impairment, no dementia' (vascular CIND) has been used to characterize subtle cognitive impairment from vascular etiologies in the absence of dementia (Hachinski and Bowler 1993; Ebly *et al*., 1995; Rockwood *et al*., 1999). The profile of cognitive impairment in these individuals has not yet been well defined. One study suggests that the preclinical stages of vascular dementia may begin more often with behavioral disturbances and delirium than memory impairment (Frisoni *et al*., 2002), while others suggest that memory impairment may be common (Meyer *et al*., 2002).

TABLE 33.2 General MCI criteria (Petersen ***et al***. 1999)

1.	Complaint (noted by individual, informant, or physician)
2.	Objective memory impairment on memory test
3.	Preserved general cognitive function
4.	Intact activities of daily living
5.	Absence of dementia

Cognitive decline occurs in the early stages of other neurodegenerative disorders. An isolated impairment in frontal-executive function can be identified prior to the onset of dementia in families with known mutations causing FTD (Geschwind *et al*., 2001; Alberici *et al*., 2004). Mendonça and colleagues (de Mendonca *et al*., 2004) retrospectively described the MCI stage of seven FTD patients and found the presence of behavioral change and frontal-executive dysfunction prior to the onset of dementia. Cognitive decline has also been described in preclinical stages of other neurodegenerative disorders such as Huntington's (Snowden *et al*., 2002; Ho *et al*., 2003), Parkinson's (Woods and Troster 2003), and sporadic Creutzfeldt-Jakob (Zarei *et al*., 2002) diseases.

A number of psychiatric disorders can also be accompanied by cognitive impairment without dementia, but the clinical profiles are not yet well defined. Cognitive decline in major depression is the most commonly studied (Lockwood *et al*., 2000, 2002; Weiland-Fiedler *et al*., 2004), but cognitive impairment without dementia in schizophrenia (Harvey 2001; Bowie *et al*., 2004) and bipolar disorder (Balanza-Martinez *et al*., 2005; Thompson *et al*., 2005) have also been described. Thus, there is a need to better characterize cognitive impairment in the absence of dementia in both preclinical syndromes and medical conditions, with particular emphasis on non-memory presentations to better relate the clinical presentation to underlying etiology.

It is also important to note that changes in cognition can be a part of normal aging. A number of studies document impairment of cognition in community-dwelling elderly individuals who do not meet criteria for MCI or dementia (Grigsby *et al*. 2002). This is not surprising given the relatively linear rates of cortical atrophy on magnetic resonance imaging (MRI), observed in studies of aging (Raz *et al*. 2005). Clearly, the differentiation from changes associated with healthy aging and neurodegenerative disease is critical for understanding the boundary between healthy and pathological aging.

Clinical Outcomes of MCI

In a review of several large longitudinal studies, Petersen *et al*. (2001) found that individuals diagnosed with amnestic MCI convert to AD at an annual rate of

between 6 and 25%, which is substantially higher than conversion to dementia in healthy elderly individuals. A recent study found that a community-based sample of elderly individuals classified as amnestic MCI were approximately 4 times more likely to progress to AD (Ganguli, Dodge *et al.* 2004). However, several studies point out that some individuals diagnosed with MCI do not progress to dementia, and some even revert to normal (Collie and Maruff, 2000; Ritchie *et al.*, 2001; Larrieu *et al.*, 2002). Patients with MCI are also at a higher risk for future functional impairment (Tabert *et al.*, 2002) and mortality (Rockwood *et al.*, 2000; Tuokko *et al.*, 2003). Likewise, individuals with vascular CIND are at an increased risk for converting to vascular dementia (Wentzel *et al.*, 2001; Meyer *et al.*, 2002).

Several studies have found that individuals with amnestic MCI are likely to have pathological AD at autopsy (Berg *et al.*, 1998; Morris *et al.*, 2001; Lambon Ralph *et al.*, 2003), thereby suggesting that amnestic MCI can represent a very early AD and not just a transitional stage between healthy aging and AD. Huang *et al.* (2002) report that the conversion rate from MCI to AD is about 14% per year. It is important to keep in mind, however, that the majority of studies focus on amnestic MCI and its relationship with AD, and the clinical outcome of individuals with non-amnestic MCI syndromes is not yet well known. Several authors have proposed that individuals who exhibit non-memory MCI will progress to disorders other than AD (Petersen, 2004). Our case of dysexecutive MCI discussed below, however, suggests that markers of AD are expressed in non-amnestic forms of MCI.

Imaging Cingulate Cortex in Amnestic MCI

Structural and metabolic imaging methods with MRI, single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have identified structures involved in MCI and the early stages of AD (see Chapter 34 of this volume). Metabolic imaging studies of early AD consistently document a reduction in rCBF in posterior association areas including the PCC and precuneal/medial parietal cortices (Haxby *et al.*, 1985; Salmon *et al.*, 1994; Jagust *et al.*, 1995; Minoshima *et al.*, 1997). These areas of hypometabolism correlate with performance on neuropsychological tests in early AD (Nobili *et al.*, 2005) and PCC hypometabolism have been documented in amnestic MCI (Nestor *et al.*, 2003). Interestingly, reductions in the posterior cingulate gyrus volume help predict which MCI patients will convert to AD (Kantarci *et al.*, 2000; Chetelat *et al.*, 2003). Huang *et al.* (2002) noted a reduction in PCC rCBF up to 2 years before the diagnosis of AD. Johnson *et al.* (1998) found that a combination of tCBF values from the cingulate gyrus, hippocampus-amygdala and thalamus, identified approximately 80% of MCI patients who converted to AD after 17 months of follow-up. Another study found that hypometabolism in the temporoparietal and PCC in MCI patients specifically with an apolipoprotein ε4 allele, predicted conversion to AD (Mosconi *et al.*, 2004). Finally, normal adults aged 20–39 who have an ε4 allele show hypometabolism in the brain regions that overlap with AD, including the cingulate cortex (Reiman *et al.*, 2004).

Co-registration of the reported sites of altered blood flow onto the medial surface in Figure 33.1 emphasizes the most vulnerable part of this region in amnestic MCI. Dorsal PCC and posterior midcingulate cortex (pMCC) are in the primary focus of damage. Thus, the posterior cingulate gyrus is an important structure to identify MCI and early AD.

Although structural MRI generally focuses on medial temporal structures in MCI (De Leon *et al.*, 1997), structural MRI methods frequently report reductions in PCC volumes as discussed in Chapter 34. Both structural and metabolic imaging may, therefore, be quite sensitive to changes in cingulate cortex that are associated with preclinical AD. More advanced structural imaging techniques, such as diffusion-tensor imaging, may better reveal the most vulnerable cingulate regions in MCI. A recent diffusion-tensor imaging of fiber tracts in MCI subjects suggested a loss of integrity of posterior cingulum bundle fibers that may reflect changes in the white matter (Fellgiebel, 2005; Jack *et al.*, 1997; Du *et al.*, 2001). Once again, a decrease in brain metabolism in the

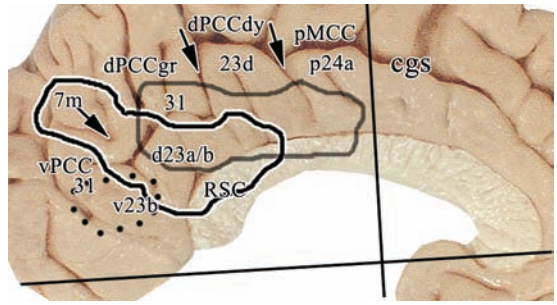

Fig. 33.1 Plot of medial surface CMRglc in three studies of MCI in relation to Talairach AC-PC line and VAC on a postmortem histological case to identify involved areas and regions: first arrow on right is at the border of pMCC/dPCCdy (dysgranular part of dPCC); middle arrow divides dPCC into dPCCdy and its granular part including areas d31 and d23; arrow on left separates dPCCgr from vPCC. Drzezga ***et al.*** (2003; dark line with white stroke) showed hypometabolism in rostral RSC, areas d23a/b, 31, and 7m. Nestor ***et al.*** (2003; light black line) showed a more rostral hypometabolism including areas d23a/b, 31, and 23d primarily and the focal damage extended into area p24a. An extensive parahippocampal site was also noted. Chételet ***et al.*** (2003; dotted line) correlated metabolism with encoding and retrieval and showed correlated CMRglc in areas v23b and 31.

posterior cingulate gyrus is particularly important for understanding MCI and early AD.

Neuropathology of Amnestic MCI

Prior to the development of a clinical definition of MCI, a number of investigators examined the brains of non-demented healthy, elderly individuals and noticed that a subgroup had sufficient senile plaques (SP) and neurofibrillary tangles (NFT), for a diagnosis of AD (Khachaturian, 1985; Katzman *et al.*, 1988; Delaere *et al.*, 1990; Dickson *et al.*, 1991; Berg *et al.*, 1993; Bouras *et al.*, 1994; Lue *et al.*, 1996; Troncoso *et al.*, 1996; Hulette, 1998; Davis *et al.*, 1999). These high-pathology controls (HPC) were thought to represent very early AD or preclinical AD, but the lack of significant cognitive impairment in the presence of AD neuropathology was puzzling.

When non-demented individuals with limited pathology are compared with non-demented individuals with AD pathology retrospectively, cognitive deficits are observed in a majority of subjects in the latter group. For example, extensive neocortical diffuse plaque formation in HPC was associated with Clinical Dementia Rating scores of 0.5 (Price *et al.*, 1991; Morris *et al.*, 1996). In a study of 31 non-demented elderly brains (CDR=0), 14 presented with possible AD according to Consortium to Establish a Registry for Alzheimer's Disease criteria, and a subset of these preclinical cases exhibited cognitive deficits in 1 or more cognitive domains based on neuropsychological testing (Hulette *et al.*, 1998). Thus clinically, the majority of HPC cases may represent subjects with MCI or may, indeed, be preclinical AD.

Over the last several years, the definition of MCI has been clarified on the basis of clinical criteria allowing prospective longitudinal studies. MCI patients appear to fall into intermediate stages in the extent and location of senile plaque and NFT pathology, compared with non-demented controls and those with mild AD. In MCI, amyloid-β peptide (Aβ) loads in entorhinal cortex were intermediate between normal and AD (Mufson *et al.*, 1999). However, there may be overlap in the extent of Aβ deposition in MCI and normal controls, but this may also occur if normal control cases include preclinical AD subjects. Cortical NFT may also differentiate MCI from normal to a greater extent than SP accumulation (Crystal *et al.*, 1988).

Recent autopsy studies of clinically characterized MCI have focused on hippocampal and entorhinal pathology. Sufficient pathology for a diagnosis of AD at autopsy was observed in a series of MCI patients, strongly suggesting that MCI is an early AD (Morris & Price, 2001). Neuron counts in the entorhinal cortex of MCI cases were significantly reduced (63.5%) in layer II (Kordower *et al.*, 2001). Similar but more modest results were observed in a second study with a 32% neuron loss in entorhinal cortex layer II in MCI patients that was inversely correlated with the extent of NFT formation and not associated with Aβ (Gomez-Isla, 1996). In contrast, despite observing entorhinal and hippocampal neuron loss in MCI, preclinical AD also did not exhibit significant losses (Price *et al.*, 2001). In response to neuron loss in entorhinal cortex and reduced input to the hippocampus, there may also be a compensatory growth or sprouting response in the hippocampus. Increased choline acetyltransferase in the hippocampus of MCI was observed relative to non-demented normals and AD (Ikonomovic *et al.*, 2003), which is consistent with findings in rodent entorhinal cortex lesion models (Cotman & Scheff, 1979; Deller & Frotscher, 1997).

Neuropathological studies have a sampling bias for hippocampal and parahippocampal cortices that does not consider neuron densities in the dPCC. Indeed, evaluating neuron densities in the cingulate gyrus presents a substantially more difficult problem than does counting neurons in easily identified islands of cells in layer II of entorhinal cortex, and in the hippocampus where laminar architecture is not as complicated as that in the cingulate gyrus. It has long been known that dPCC experiences early and substantial neurodegeneration in AD (Vogt *et al.*, 1991, 1998). Moreover, these latter studies suggest different laminar patterns of neurodegeneration that certainly support the hypothesis of AD subgroups and are not easily interpreted in terms of a single disease progression (Vogt *et al.*, 1999). It will be necessary to understand the laminar patterns of neuron losses in amnestic MCI, so the heterogeneity in cell loss can be understood in terms of the earliest stages of AD. Moreover, as predicted from studies of dPCC, it is likely that more than one subgroup/subtype of AD is expressed in dPCC, and this view is supported by our assessment of a case of dysexecutive MCI.

Dysexecutive MCI and AD: Posterior Cingulate Damage and Visuoconstructional Deficit

One of the symptoms of damage to PCC is impairment of visually guided movements and orientation in local and global space as discussed in Chapter 13. Although strokes in this region are the primary basis for such a conclusion, AD also produces damage here and it supports a similar conclusion. Giannakopoulos *et al.* (1998) evaluated NFT in AD with a multivariate model and found statistically significant relations between NFT in area 24 and ideomotor apraxia, and those in area 23 with visuoconstructional apraxia. It is not surprising that impairments in PCC are associated with visuospatial

aspects of movement. We assessed the differential functions and circuitries of the dPCC and vPCC cortex with fluorodeoxyglucose (FDG)–PET, a re-analysis of the literature based on this dichotomy (Vogt *et al*., 2006), and differences between the dorsal and ventral visual streams and the dPCC and vPCC, respectively, were demonstrated. The dPCC, including area 23d, had highly correlated activity with MCC including the cingulate premotor areas, while vPCC did not have such correlated activity. Chapter 13 extends these views with new FDG–PET findings and concludes that a general sensorimotor orientation is possible in this region, and it correlates with the connectivity with caudal cingulate premotor area. It appears that dPCC is a pivotal link for orienting the body in space and plays a key role in visuomotor integration. These functions are compatible with some of the non-memory impairments observed in MCI and may explain a substantial part of the early executive symptoms in these cases. We must consider the level of involvement of PCC, posterior MCC and the caudal cingulate premotor area in MCI, and consider the possibility of the presence of a second subgroup of MCI that generates a second subgroup of AD.

Drzezga *et al*. (2003) observed glucose hypometabolism relatively restricted to posterior cingulate and medial parietal cortices. Patients that converted to AD 1 year later had an additional glucose hypometabolic site in prefrontal cortex; and they suggested this is associated with the transition from MCI to AD. Nobili *et al*. (2005) correlated brain perfusion with performance on a number of behavioral tasks in very mild AD and observed a high correlation between reduced perfusion and constructional apraxia in PCC and precuneal cortex.

Neuropathology in Dysexecutive MCI

Assessment of the brains of carefully characterized and longitudinally followed subjects with MCI, with short intervals between last clinical assessment and death will be critical for improving our understanding of early events in AD pathogenesis. Further, subjects with isolated cognitive impairment in other domains, such as executive function, language or visuospatial ability, may also transit into AD or possibly other dementias; and postmortem assessment of these cases will, in the long run, uncover the etiologies of many dementias.

A subset of HPC cases may represent preclinical AD and are without signs of memory impairment or cognitive decline (Goldman *et al*., 2001). Clinicopathological studies of non-demented elderly control brains reveal a subset of preclinical cases with significant amounts of frontal Aβ (Morris *et al*., 1996; Troncoso *et al*., 1996; Haroutunian *et al*., 1998). A unique study of a mother and her daughter provided further evidence of the importance of Aβ early in AD pathogenesis. The mother was clinically diagnosed with AD and the daughter, despite being cognitively intact at the age of 47 years, already had significant SP pathology suggesting that Aβ accumulates for many years before symptoms, and is an early part of AD pathogenesis (Troncoso *et al*., 1996). The results of another autopsy series also showed that a subset of non-demented individuals with brains that developed sufficient pathology for an AD diagnosis (8/124 subjects; Lue *et al*., 1996). Interestingly, Aβ in the form of SP and insoluble Aβ did not distinguish preclinical AD from normal cases, nor did the amount of soluble Aβ. Furthermore, soluble Aβ was correlated with steady state levels of synaptophysin, a marker for the extent of synapse loss (Lue *et al*., 1999). Higher amounts of soluble Aβ were associated with lower synaptophysin levels. There was also a lack of significant inflammatory response typically observed in AD suggesting that inflammation may be a later stage event in AD pathogenesis (Lue *et al*., 1996; Akiyama, 2000).

Despite changes in the hippocampus and entorhinal cortex (e.g., neuron loss, compensatory responses) in MCI, few neuropathological changes have been observed in neocortex, with the possible exception of Aβ deposition in the form of diffuse plaques (Price *et al*., 1991; Morris *et al*., 1996, 2001). For example, measures of frontal pathology including soluble α-synuclein, myelin basic protein, ubiquitin, synapse markers, Aβ40, Aβ42, and PHF-tau show no differences between MCI and healthy elderly controls (Wang *et al*., 2001, 2004). A lack of frontal pathology in clinically characterized MCI patients may reflect the focus on amnestic MCI and memory networks.

Executive Impairment in an MCI Case: The 'Frontal' Variant

Research has generally focused on amnestic MCI and the entorhinal cortex in both clinical and neuropathological studies due to the expectation that AD is fundamentally amnestic, and the general failure to appreciate the role of PCC and RSC in memory. As many MCI cases convert to AD, the dPCC has an established role in memory and visuocontructional deficits in AD, and a frontal variant of AD has been described with damage to dPCC (Johsnon *et al*., 1999), we explore a unique case of early executive impairment without amnesia. As part of our continuing interest in atypical presentations of dementia, we described a 68-year-old, non-demented woman who had an isolated impairment on tests of executive function; trailmaking test, and preserved memory, visuospatial, and language abilities (Johnson *et al*., 2004). She was being followed as a part of a healthy aging cohort and scored 29/30 on the Mini-Mental State Examination (Folstein *et al*. 1975). Although detailed information was not available to officially diagnose her

with MCI, we reviewed medical records that suggested there was no obvious change in activities of daily living, and she was still driving an automobile near the time of her death. We proposed that an isolated impairment on tests sensitive to the frontal lobe may represent a frontal-executive presentation of MCI. This individual provided a unique look into an isolated cognitive impairment because she passed away prematurely from a myocardial infarction. The following postmortem studies, therefore, follow final testing by 20 months.

Frontal and temporal pathology

Consistent with the clinical profile and neuropsychological hypothesis based on executive impairment, the extent of NFT and Aβ formation was highest in the mid-frontal cortex relative to other cortical regions including temporal and hippocampal, parietal, and occipital cortices. Moderate to dense NFT in the entorhinal cortex and subiculum were seen with a relative sparing of the area CA1 of the hippocampus. Accumulation of phosphorylated tau protein (AT8 antibody) within a subset of hilar neurons had a morphology that was consistent with a sprouting response. The cell bodies, apical dendrites and terminals were all positive for abnormal tau. A similar observation has been reported in adults with Down's syndrome prior to extensive AD pathology, and hypothesized to represent a possible re-expression and accumulation of fetal tau (Head *et al*., 2003). This suggests a possible compensatory response to progressive AD pathology in the entorhinal cortex, and may be linked to the relatively preserved memory function in this case with isolated executive impairment (Masliah *et al*., 1991a, b).

The present case raises an important question. Where did the pathological changes begin in this case? Figure 33.2 shows the pivotal distinction between entorhinal cortex and dorsolateral prefrontal cortex (DLPFC) for three markers of AD. All three have a higher level of pathology in the frontal than entorhinal cortex. In contrast to predictions about the progression of AD based on ascending Braak stages (Braak & Braak, 1997), greatest neurofibrillary degeneration could not have occurred first in the transentorhinal cortex because more is present in prefrontal cortex. Indeed, the highest level of AT8-immunoreactive neurites and neuritic plaques were in the frontal area 8. This theme continues for early PHF and Aβ peptide deposition as also shown in Figure 33.2.

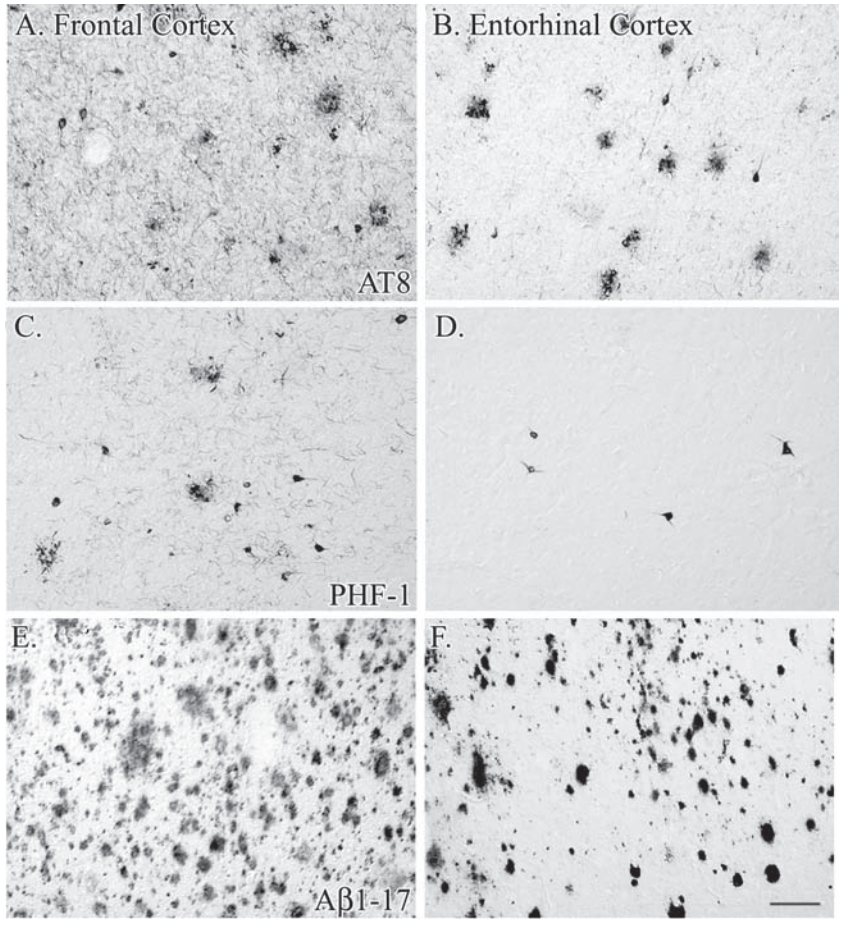

Fig. 33.2 Comparison of heavy deposition of NFT (AT8, PHF-1) in dorsolateral prefrontal cortex versus entorhinal cortex in a subject with isolated executive impairment; A similar pattern of AT8 immunoreactivity mainly in clusters of dystrophic neurites. Mature tangle formation visualized using anti-PHF-1 antibody and 6E10 (Aβ1-17) immunolabeling of SP in the mid-frontal gyrus and entorhinal cortex. Aβ was diffuse and was most extensive in the frontal cortex. Scale bar, 100 μm.

Cingulate neurofibrillary damage: The 'posterior cingulate' variant

The surprising feature of our own report of isolated executive impairment associated with frontal neuropathology is that the highest density of neurofibrillary degeneration was *not* in the frontal lobe but rather in PCC. Figure 33.3 demonstrates the region of highest AT8 immunoreactivity in the frontal lobe in this case (area 8) and compares it with a photograph through area 23d (subregion dPCCdy). The density of AT8 staining in area 23d is much higher than that in area 8 (see Fig. 33.4 for location of sample on medial surface). How can there be such a high level of PCC damage in a case with impaired 'frontal' executive functions? It appears that we lack precise tests for PCC damage; the cognitive impairment was not detected until the case had progressed to a stage where frontal lobe damage and dPCC function appears to overlap with that of mid-frontal cortex.

The greatest density of neurofibrillary damage in dPCC/pMCC suggests that this is the site of the first lesion in this brain; assuming that the lesion markers build over time. How do we explain the paradox of first lesion in dPCC and pMCC in an executive impaired patient that was presumed to have primarily, an early and dense prefrontal damage? Sensitive measures of dPCC function are not available and its damage may go undetected in neuropsychological examinations, and demonstration of executive impairment may come when the MCI patient is converting to AD. In addition, some of the neuropsychological consequences of dPCC/pMCC damage may be misconstrued as 'prefrontal'

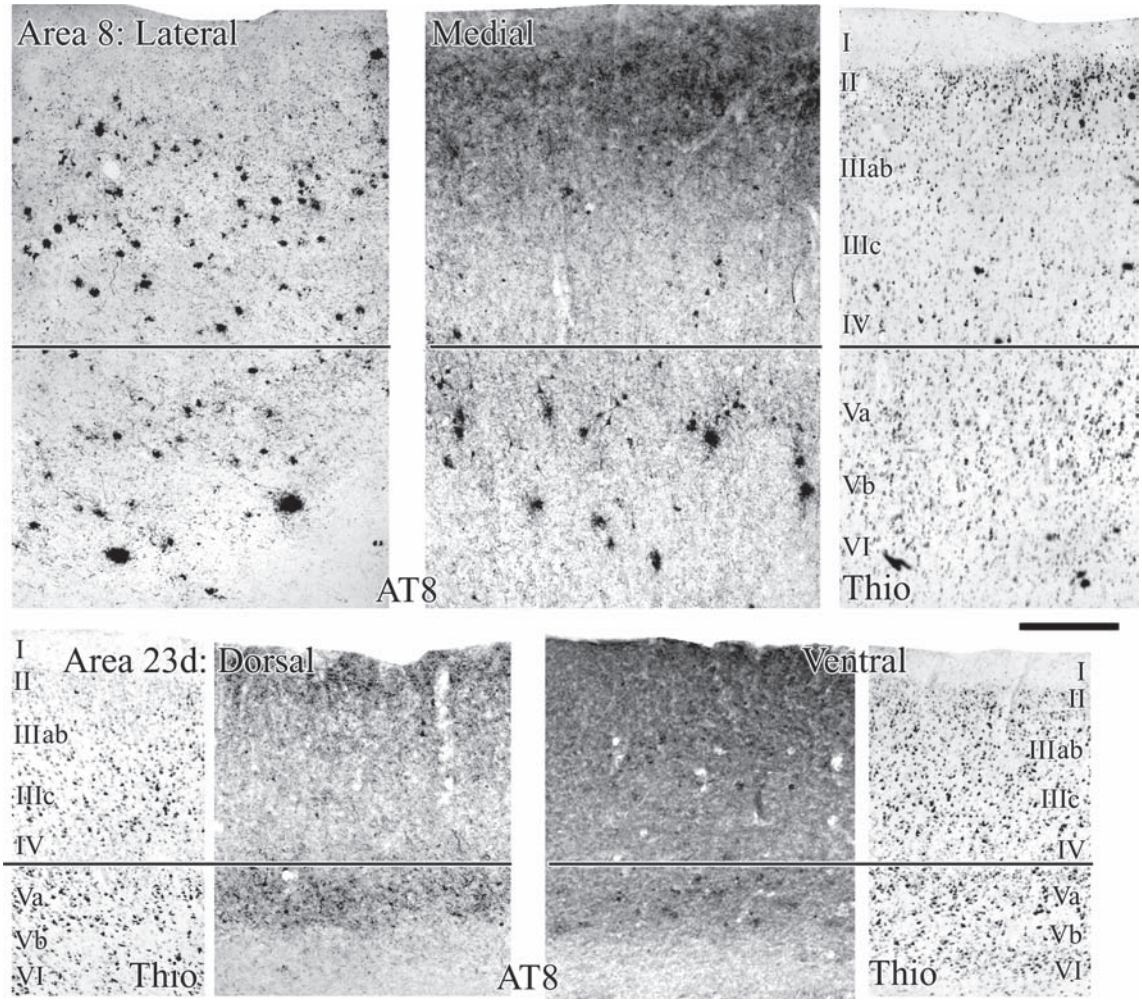

Fig. 33.3 Area 23d on the dorsal and ventral banks of the splenial sulci (spls) has more neurofibrillary degeneration than does area 8 laterally and medially. The location of medial area 8 is shown in the next figure with an asterisk. Horizontal lines are aligned at the layer IV/Va border. Thio, thionin; Scale bar, 200 μm.

when in fact there is greater damage elsewhere in the brain. This suggests that the role of dPCC in executive decisions needs modification.

The focal nature of cingulate neurofibrillary degeneration in this case is startling as shown in Figure 33.4. The AT8-immunoreactive neuropil threads are most dense in layers I-III, but a second band in layer Va is also apparent. Intra-areal differences can be striking as in area 23d above and below the splenial sulci (spls) and above and below the cgs in area a24′ (level 4). Also quite notable is almost complete lack of involvement of areas 32 and 32′. Indeed, all of ACC is 'relatively' free of neurofibrillary degeneration. Finally, although the neuropil threads are extensive, there are almost no somatic NFT in this region as is true for DLPFC.

Cingulate Aβ peptides and 'non-overlap' with neurofibrillary degeneration

Most neuropathological studies of AD and its prodromal forms seek to identify the sequence of events that link early deposition of pathology markers to neurodegeneration. Among the most popular theories is that Aβ peptides induce tau phosphorylation (Näslund *et al.*, 2000; Williamson *et al.*, 2002) and seed subsequent neuropil thread formation. This MCI case provides a unique opportunity to consider this problem because the distributions of markers and neuron loss in the cingulate gyrus are so early and focal. An early linkage between neurofibrillary degeneration and Aβ peptide deposition is weak at best, in this case.

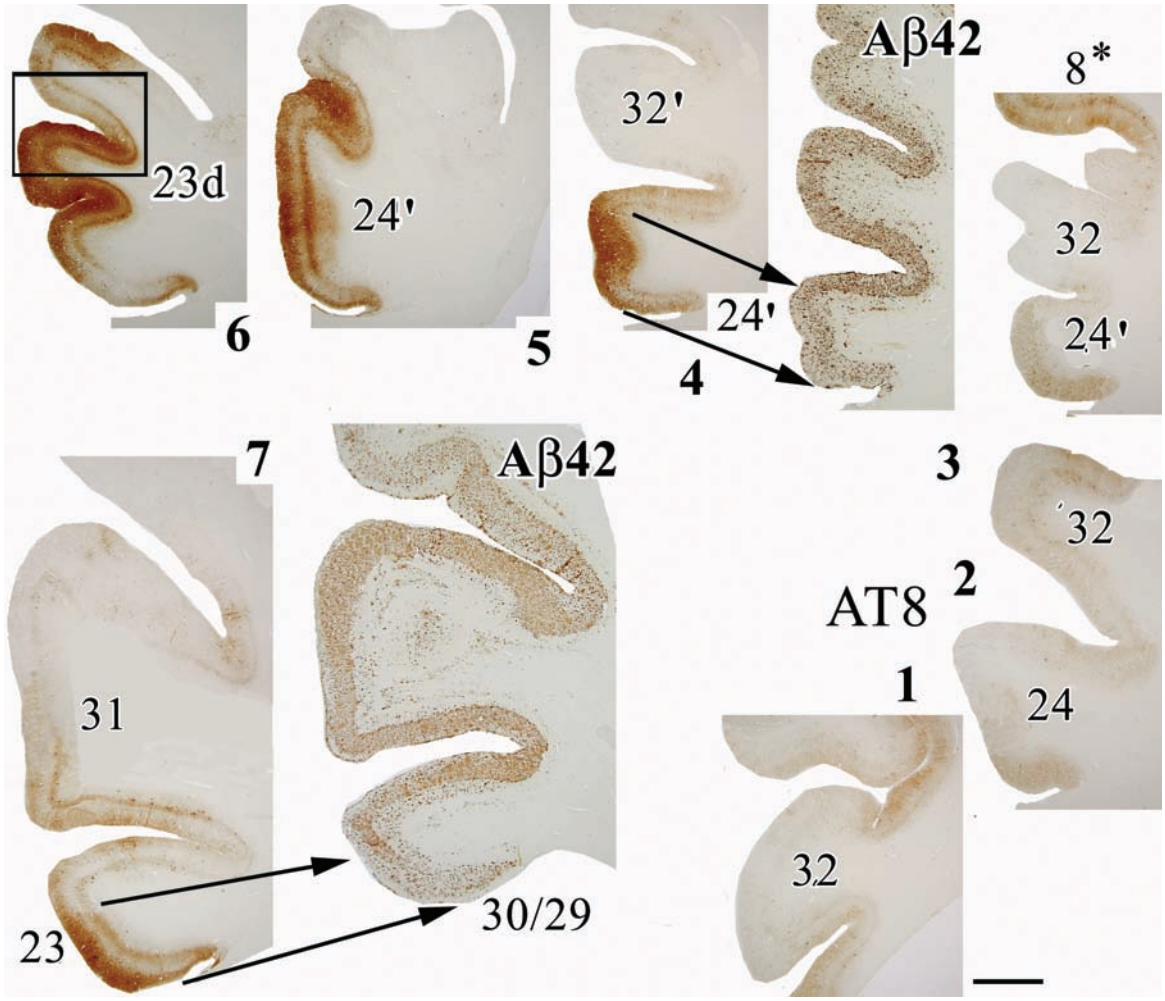

Fig. 33.4 Distribution of neurofibrillary degeneration (AT8 immunoreactivity) and a comparison with Aβ42 reactions at two levels (next figure locates levels 1-7 and surface features on medial surface). In addition to demonstrating the primary focus of pathology in the dPCC/area 23d and pMCC (area 24′), the two Aβ42 sections show a striking 'mismatch'. At L7, e.g., highest AT8 is in areas 23a and 30, while the Aβ42 marker is highest in area 23c in the sulcus and it extends onto the gyrus in area d23b. A similar differentiation is present in area 24′ in L4. The asterisk at area 8 is where the sample from Figure 33.3 was photographed for medial area 8. Scale bar, 5 mm.

Figure 33.5 shows that the highest levels of Aβ42 are in dorsal ACC and MCC and there is only a small focus in dPCC above the spls. Low levels of Aβ42 occur along most of the ventral part of cingulate gyrus as marked with arrowheads in Figure 33.5. In most instances, the places where there are low levels of Aβ42 are the places where neuropil threads are the highest. Specific points of non-overlap include the following: 1) The boxes on level 6 of both Figures 33.4 and 33.5 show area 23d dorsal and ventral to the spls. Cortex above has a high density of Aβ42 and low neuropil thread density, while cortex on the ventral bank has the opposite profile. 2) In level 7, there is a high density of neurofibrillary degeneration in area d23a/b and retrosplenial areas 29 and 30, while the deposition of Aβ42 is low. 3) Figure 33.5 has a box in level 4 that emphasizes the high level of Aβ42 in area a24c′ in the cingulate sulcus (cgs) and much less on the gyral surface, while the inverse pattern can be observed in Figure 33.4 at Level 4. 4) The external cingulate gyrus comprising area 32′ has a high level of Aβ42 and almost no AT8 immunoreactivity. The same can be said for most of the ACC. Thus, the hypothesis that Aβ42 deposition is closely associated with tau phosphorylation is not supported for this case of early dysexecutive MCI, although it may still act as a trigger event and not follow the progression of deposition.

Cingulate neurodegeneration

Localizing neocortical neuron losses in neurodegenerative diseases is a tricky balance between locating the damage topographically and using the remaining neurons to evaluate what is left of particular layers and areas. Co-registration of disease markers to the thionin-stained sections increases the detection of laminar borders as shown in Figure 33.6, and identification of area 23d and other dPCC areas is based on Vogt *et al.* (2006). In this figure, co-registration was performed with two Aβ peptides to the thionin-stained sections, on the ventral and dorsal banks of the cgs at level 4 to show area a24c′, and above and below the spls at level 6 to show area 23d. Co-registration of thionin with disease markers also provides a means of co-localizing possible

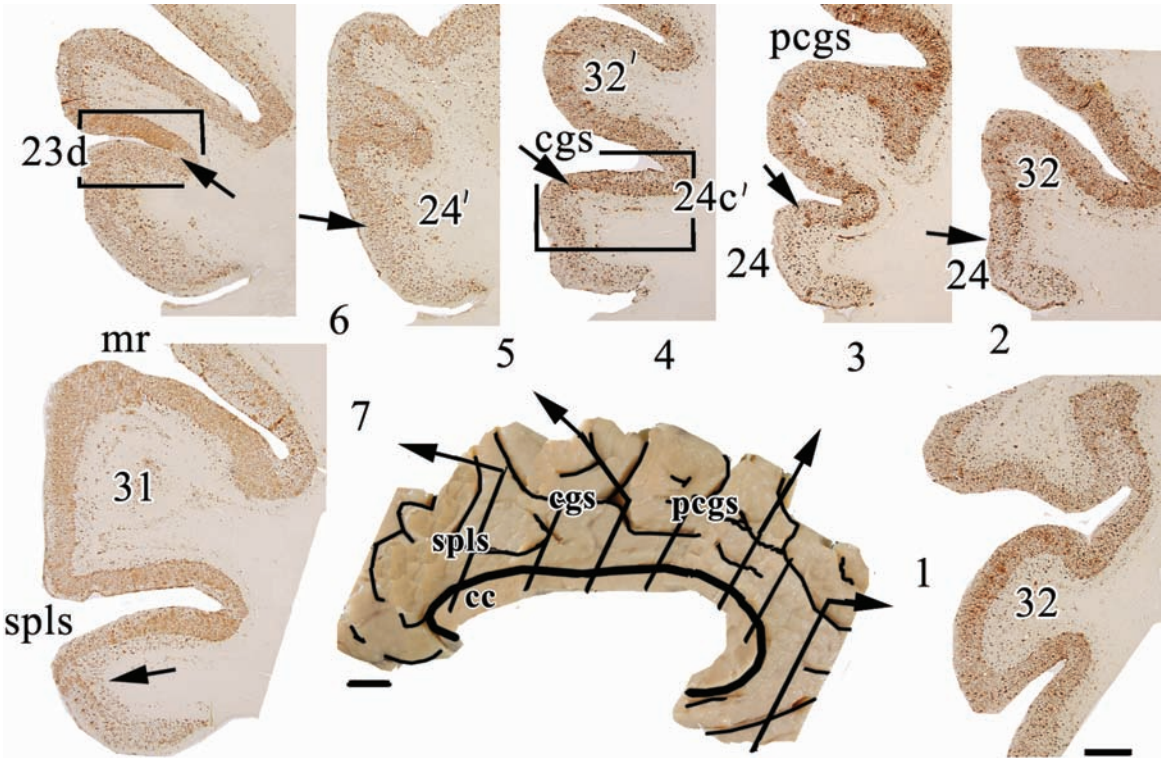

Fig. 33.5 Distribution of Aβ42 throughout the cingulate gyrus; numbered levels as in the previous figure. The Aβ42 antibody is more extensive in dorsal parts of the cingulate gyrus than neurofibrillary degeneration (AT8 in previous figure) which is more dense in ventral parts of the gyrus. The arrowheads in each section locate points of transition in the density of Aβ42 to enhance comparison with AT8 immunoreactivity in the previous figure. cc, corpus callosum; cgs, cingulate sulcus; pcgs, paracingulate sulcus; spls, splenial sulci; Scale bars; left, 1 cm, right, 4 mm.

triggers of neuron death. To the extent that a particular marker overlaps with profound neuron losses, such a linkage may indicate a mechanism of cell death.

The loads of Aβ40 are generally quite low in this case in the cingulate gyrus, and are comprised mostly of dense-core SP. Although, there are more neurons in layer III and neuron loss occurs there, layer V has heavy neurodegeneration in area 23d (L6) and there is almost no Aβ40 in this layer. To the extent that neurotoxic events associated with Aβ peptide deposition is occurring in the cingulate focus, it is more likely associated with Aβ42.

At Level 4, there is high Aβ42 in layer III and greatest neuron losses in this same layer as emphasized with the parenthesis. There are also higher levels of Aβ42 in the dorsal than ventral banks as can be seen at lower magnification in Figure 33.5. Cortex at Level 6 is mainly of area 23d and appears to be substantially further along in the degenerative process than that in rostral cortex. Although, Aβ42 appears at the same levels as in L4, it is highest in the dorsal bank of the spls. The two asterisks emphasize neuron losses in layer III, also extending into layer II. It is possible that Aβ42 is neurotoxic in this layer.

Deep layers V and VI are most damaged in area 23d of L6 and this is shown with the double-headed arrows in Figure 33.6. Although, some neurons are missing in L4, there is almost no evidence for a layer VI in L6 and layer V is almost completely obliterated. It is also noteworthy that the highest loads of Aβ42 in L6 are in layers I-V, and this is greater than in L4. These associations and neuron losses suggest that the earliest and greatest neurodegeneration occurs in layers V and VI of area 23d; and to the extent there is progression in this process, it extends rostral to the primary site to include MCC though at a lower level of overall neuron loss.

Although there is a secondary site of neurofibrillary degeneration in retrosplenial cortex, the ventral PCC appears to be relatively free of pathology. The general integrity of vPCC in amnestic MCI is supported by a recent fMRI study showing that vPCC has an intact response during an autobiographical, self-appraisal task (Ries *et al.*, 2005). A similar finding is predicted for the dysexecutive subgroup of MCI.

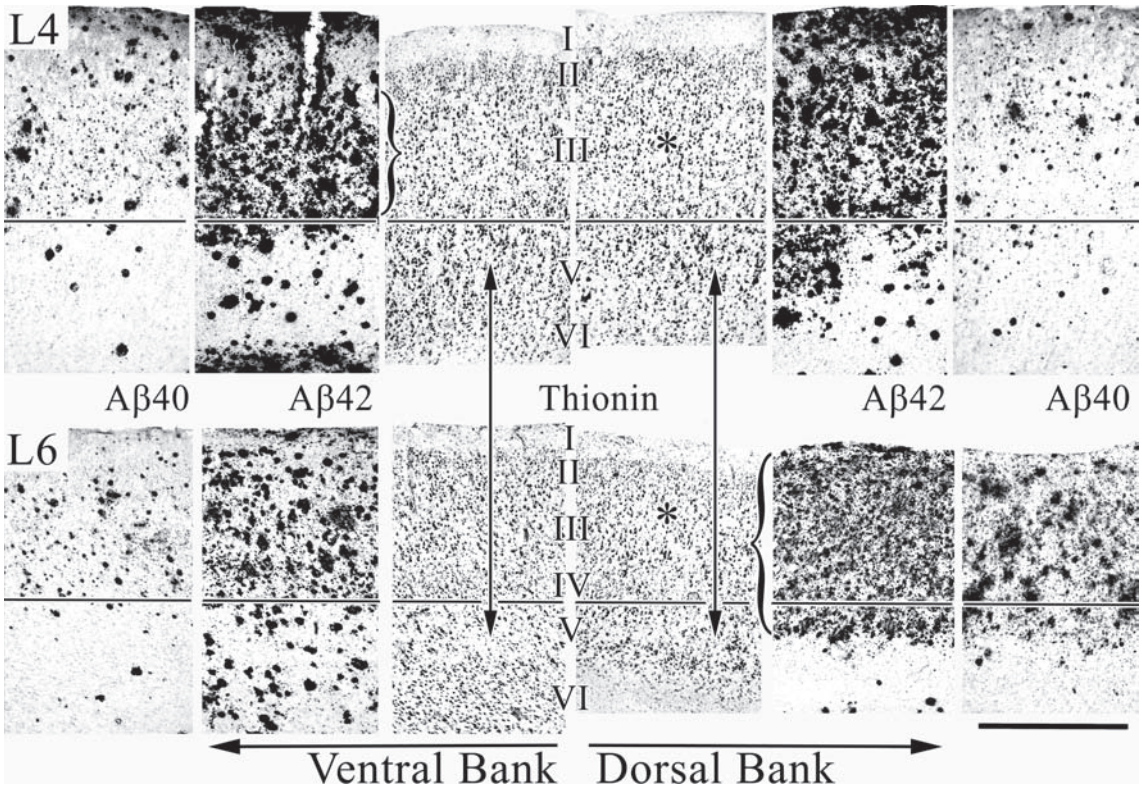

Fig. 33.6 Co-registration of Aβ peptides to thionin-stained sections on the ventral and dorsal banks of the cgs at L4 for the area p24c′ and the spls at L6 for the area 23d. Key links include L4 where high Aβ42 is in layer III and greatest neuron losses in this same layer (parenthesis) and higher Aβ42 load in the dorsal than ventral banks. L6 is further along in the degenerative process. Although Aβ42 load is the same as above, it is highest in the dorsal bank of the spls. The two asterisks emphasize neuron losses in layer III and extending into layer II and the double arrows emphasize the profound neuron losses in layers V and VI in area 23d compared with area 24′. The highest loads of Aβ42 are in layers I-V (parenthesis) at L6. Scale bar, 100 μm.

MC1 in MCI: Early Conformation of Tau in Primary and Secondary Foci

One of the earliest alterations in tau proteins in AD, is a conformational change (Weaver *et al.*, 2000). Immunoreactive neurons and neurites for an antibody to this conformation were demonstrated in this study in hippocampi from AD cases at Braak I and II stages. This early conformational change is of particular importance for two reasons. First, although, the primary focus for the dysexecutive MCI case was in dPCC and pMCC, we are interested in identifying secondary sites of involvement to provide keys to the next stage of neurodegeneration; i.e., what did the future hold for this patient had she not died. Second, as this patient could not be diagnosed with AD and had a unique pattern of disease markers, and the MC1 antibody is unique to AD (Weaver *et al.*, 2000), it provides diagnostic support that this subject would have converted to AD.

In contrast to the hippocampus in AD (Weaver *et al.*, 2000), no MC1-positive neuronal somata were seen in the cingulate gyrus. Only small balls of neurites were present as well as some solitary and extended neuritic profiles. The neuritic balls were about 50-60 μm in diameter and they were most dense in area 23d in the core of the primary lesion, where a bilaminar pattern occurred in layers III and V. Figure 33.7 shows samples from four levels and links them with the AT8 immunoreactive sections. We suspect the neurites in these balls to be primarily axons because injections of human immunoglobulins into monkey cerebral cortex generates MC1 immunoreactivity in axons only, as determined with light and electron microscopy (Bouras *et al.*, 2003).

Figure 33.7 shows most MC1 neuritic processes in the primary focus in level 6 in layers III and V on the ventral bank of the spls where AT8 is also most dense. In contrast, on the dorsal bank, there are almost no MC1 immunoreactive profiles. Interestingly, there were scattered MC1 neurites throughout the entire cingulate gyrus except in large parts of areas 32 and 32′. A dorsal part of area 32 (arrow to L1 in Fig. 33.7) showed a low level of AT8 reactivity and suggested a secondary site of degeneration was forming. If this were true, it should also express substantial MC1. Indeed, the density of MC1-immunoreactive processes was quite high in this area. Also, area 8 had quite a dense complement of MC1-positive processes to match with its reasonably moderate density of AT8 staining. We assume the progression of neurodegeneration associated with tau phosphorylation, was in the early stages in these secondary sites.

Cell-Cycle Reentry Mechanism of Neurodegeneration

Demonstration of DNA replication in AD suggested a mechanism for neurodegeneration (Yang *et al.*, 2001).

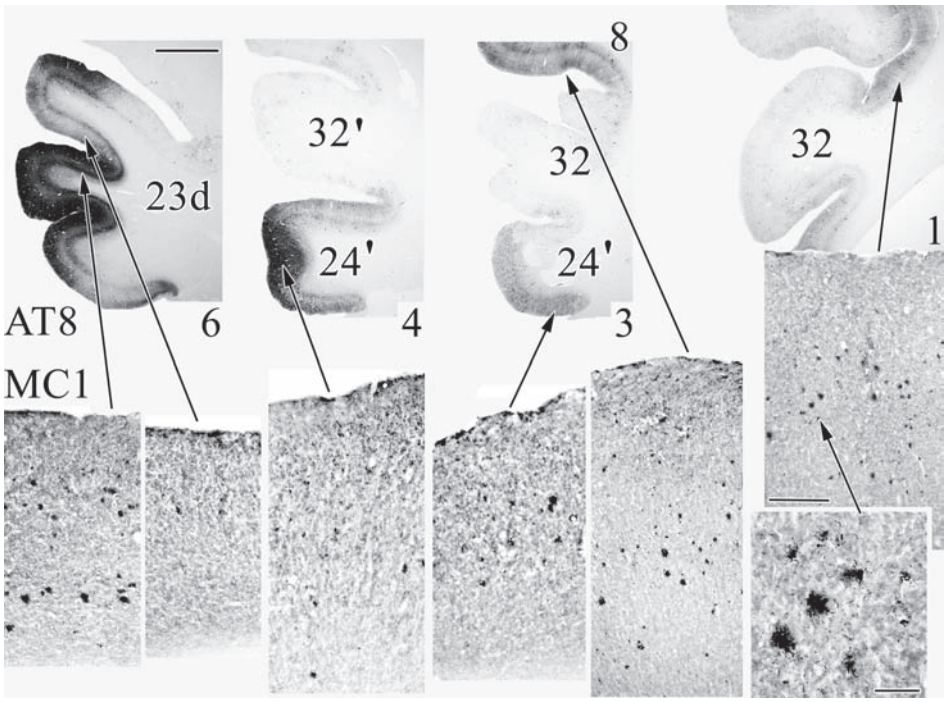

Fig. 33.7 Localization of MC1 antibody in relation to AT8 in Figure 33.4. Neuritic balls are shown at high magnification for area 32 on far right. Though greatest MC1 activity was in primary focus, secondary foci such as that in area 32 that also have moderate or low AT8 staining also had MC1-positive neuritic balls. Scale bars: 5 mm/AT8; 500 and 100 μm/MC1.

It was suggested that the reentry of neuron into S phase was a lethal process, and cell cycle proteins provide useful markers of this aborted attempt to initiate mitosis. Herrup and Busser (1995) showed that target-deprived neurons synthesized cell cycle enzymes including a marker of S-phase termed proliferating cell nucleus antigen (PCNA) and incorporated bromodeoxyuridine into DNA before dying. Thus, cell cycle proteins appear in neurons at risk of death. Yang *et al.* (2003) extended these findings by showing that hippocampal, entorhinal and basal forebrain neurons express cell cycle proteins in early AD and MCI. Although, a wide variation of immunopositive neurons were seen, it was concluded that neuron death in AD has as its root cause, an ectopic reentrance into the cell cycle and proposed that this may be a unified mechanism of cell loss.

In view of cell cycle markers such as PCNA as being an early marker of neurodegeneration in MCI, we prepared 125 sections immunoreacted for PCNA through the cingulate gyrus of the present case. The goal was to identify other vulnerable areas in the cingulate gyrus that may be in the earliest stages of neurodegenerative activity; i.e., another focus forming somewhere else in the cingulate gyrus that would provide a clue to the next stage of cell death. Control sections minus the primary antibody had no staining (not shown) and all sections were reviewed to identify regions outside the primary focus that were at risk of neuron death.

In most sections, there were 4–10 heavily labeled microglia and Figure 8A shows one example of these cells, and this suggests a uniform activation of microglia. More importantly, the search for PCNA-positive neurons showed only two sites of activity. Both sites were close to or part of regions of severe pathology already discussed above and shown in Figure 33.8. Review of the secondary sites in dorsal area 32 at level 1 showed no PCNA-positive neurons. As this latter site had MC1 and AT8 immunoreactive neurites and was clearly involved in a secondary stage of neurodegeneration, there does not appear to be a particular value to studying PCNA expression for early cell death in the cingulate gyrus.

We conclude that the cell cycle protein PCNA does not provide clues to the early and emerging pathology in the cingulate gyrus of a prodromal AD case. Although, Yang *et al.* (2003) could conclude that the cell cycle theory offered 'a single unified mechanism of cell loss,' this conclusion might be linked to the sampling procedure that emphasized medial temporal cortex, and did not consider regions with a highly variable cell loss such as the cingulate gyrus. To the extent that this MCI case might proceed to AD, the PCNA marker does not provide insight into the next region that will suffer damage.

Primary Cingulate Focus and Its Progression in the Context of Prodromal AD

MCI is a clinically heterogeneous syndrome characterized by a variety of symptom profiles. The majority of MCI research is currently focused on the amnestic subgroup with a relatively selective decline in memory. However, it is increasingly recognized that MCI may involve non-amnestic cognitive domains and it is an important syndrome because of the risk for conversion to dementia, functional impairment, and mortality. However, it should be kept in mind that some individuals diagnosed with MCI do not progress to dementia, and some even revert to normal. The pivotal role of cingulate cortex in cases that progress to AD is made by Huang *et al.* (2002), who subtracted blood flow images of stable MCI cases from those with progressive MCI. Their cingulate region of reduced blood flow is shown in Figure 33.9 and represents a general change that is not determined by a specific cognitive impairment. Thus, while MCI is framed as a preclinical stage

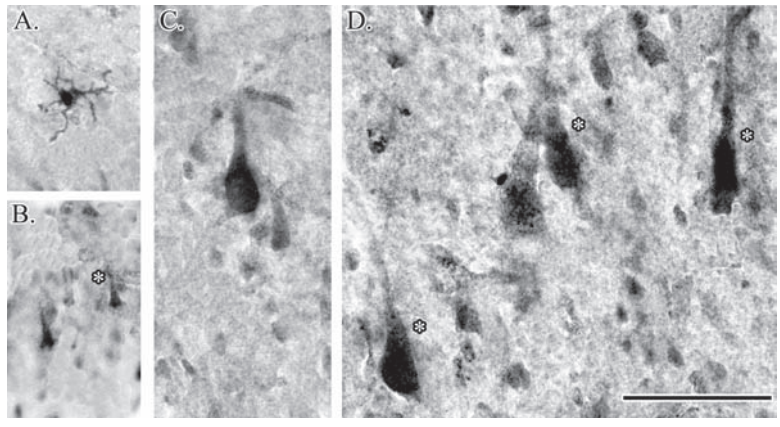

Fig. 33.8 PCNA-immunoreactive cells in the cingulate gyrus. A. Example of activated microglial cell found throughout the gyrus. B. Small neurons in layer II (e.g., at asterisk) and larger ones in layer V on the ventral bank of the spls (C.) and large neurons in layer V on the dorsal bank of the spls in area 23d. (D., asterisks) Scale bar, 200 μm.

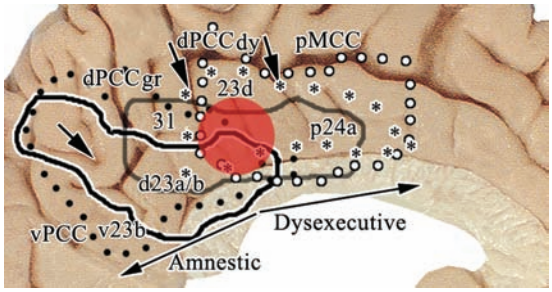

Fig. 33.9 Primary cingulate focus in studies of MCI: Red circle in area 23d. This is a conjunction analysis based on Figure 33.1 and a few additional studies including the present case: 1. Asterisks, present case; 2. White dots, MCI progressive cases of Huang ***et al***. (2002); 3. Gray line, Nestor ***et al***. (2003); 4. Black line, Drzezga ***et al***. (2003); and 5. Reiman ***et al***. (1996). The point at which all studies overlap is the primary and common site of cingulate damage in MCI and is shown in red including part of area 23d. We hypothesize that at least two trends emerge as cases progress to AD; one trend with amnestic features progresses caudally and another trend with dysexecutive features progresses rostrally to engage ever more of the frontal lobe.

of AD, it is likely that most neurodegenerative diseases will have an MCI stage once earlier detection is possible. More importantly, to the extent there are multiple subgroups and possibly subtypes of AD, there will likely be many prodromal MCI forms of AD. The linkage between dysexecutive MCI and the frontal variant of AD provides a vivid example of this possibility. Let us consider this dysexecutive MCI case in the broader context of imaging studies of MCI and its progression to AD.

The MC1 immunoreactivity in the present case suggests that it is a prodromal form of AD rather than stable MCI, because this particular conformational state of tau is present only in AD. The highest level of neurofibrillary and neuron degeneration in area 23d suggests this is the earliest site of damage is dPCC. Although, the prefrontal cortex, including medial area 8, has significant damage and may have contributed to the dysexecutive outcome, we propose that all markers indicate the primary site of focal damage was in area 23d with some extension rostrally into area p24′. Secondary sites of degeneration were associated with less profound neuron losses, high MC1 expression, low levels of AT8 immunoreactivity and almost no expression of Aβ42. These secondary sites include a small part of dorsal area 31, retrosplenial cortex, and a dorsal part of area 32. The secondary sites generally suggest the disease is progressing in a rostral direction which is consistent with the notion of an executive impairment. Moreover, this may itself be the prodromal form of the frontal variant of AD (Johnson *et al*., 1999, 2004; Vogt *et al*., 2000).

The present observations suggest a progression of events in the cingulate gyrus that may precede damage in the DLPFC. As the neurofibrillary damage is greatest in dPCC and pMCC, we assume at this time that this is the first focus of brain damage. It also appears that Aβ42 is closely associated with neurodegeneration mainly in layer III. Interestingly, although there is extensive neurofibrillary degeneration in layers V and VI of areas 23a/b/d and there is a relatively close linkage with Aβ42 and neurofibrillary degeneration in these areas, we assume that this is the site of first damage. It appears to spread into layers III and II and extend rostrally into pMCC and extending even into anterior midcingulate cortex (aMCC) and the frontal lobe.

A conjunction analysis of this case in the context of imaging studies of MCI leads to the conclusion that there are at least two trends in the progression of MCI; an amnestic trend caudally that merges with damage in parahippcampal and hippocampal cortices and a dysexecutive trend rostrally that merges with damage in prefrontal cortex. The relevant imaging studies and our case were co-registered with landmarks including the corpus callosum, cingulate and paracingulate sulci, the caudomedial lobule, and the vertex of the superior parietal and frontal gyri as shown in Figure 33.9. It is interesting to note that the Huang *et al*.'s (2002) site of reduced rCBF associated with progressive MCI was not limited to an amnestic population. The Huang site also most closely parallels the site of greatest neurofibrillary damage in our dysexecutive MCI case as shown with asterisks in the figure.

The region in red in the dPCC in Figure 33.9 is the place that is involved in all studies of MCI; that is, it is the site of greatest overlap. This cortex is part of area 23d and it likely represents a very general first site of damage in most if not all cases of MCI. This does not mean, however, that damage to area 23d is the same in all cases of MCI as there may be different laminar patterns of neurodegeneration and it does not mean that disease progression follows a single spatial course in the cingulate gyrus.

Based on the distributions of lesion markers and neurodegeneration in the primary and secondary sites of the dysexecutive MCI case, we hypothesize that this case is progressing in a rostral direction as shown by the arrow in Figure 33.9. A second progression could involve the amnestic cases and extends caudally as indicated by the second arrow pointing ventrally toward the hippocampal formation. As a frontal variant of AD has been discussed with significant alterations in executive function including aggression (Johnson *et al*., 1999; Vogt *et al*., 1999), it is a short step to the conclusion that dysexecutive MCI represents a prodromal form of the frontal variant of AD (Johnson *et al*., 2004).

The issue of MCI progression and linkages to subgroups of AD needs to be taken one step further. We previously evaluated laminar patterns of neurodegeneration dPCC in AD (Vogt *et al.*, 1998). Based on a multivariate model we observed five subgroups. The model included neuron densities in each layer and it showed that each subgroup had a full range of disease progression suggesting further independence of the case subgroups. We predict there will be at least five subgroups of MCI that form the prodromal stages for each of the AD subgroups based on laminar patterns of neurodegeneration.

Visuoconstructional Deficit: Key Symptom in Dysexecutive MCI Associated with dPCC Damage

It is important to recognize that although our subject had impaired Trail making, she did not have a generalized loss of visual orientation as would be predicted from cases of AD with damage in dPCC. Nevertheless, this case raises the question of the extent to which damage to dPCC may contribute to impairments in visually guided motor function. Chapters 1 and 13 of this volume consider in detail the contributions of this subregion to visuospatial function and its interactions with the cingulate premotor areas. Furthermore, there is a subgroup of AD with visuospatial deficits (Martin, 1990) that likely experience first damage in dPCC and it is well known this subregion is glucose hypometabolic in amnestic MCI (Minoshima *et al.*, 1997; Chapter 34).

Constructional apraxias are well known in AD and are evaluated by having the patients draw pentagons. A drawing disturbance without general impairment of intelligence, visual, or motor capabilities results from parietal lobe lesions (Zadikoff & Lang, 2005), although the specific role of PCC is not well appreciated. NFT in dPCC are significantly correlated with constructional apraxia in AD (Giannakopoulos *et al.*, 1998) and this group also observed a correlation between NFT in dPCC and spatial disorientation in AD (Giannakopoulos *et al.*, 2000). Finally, spatial disorientation is correlated with glucose hypometabolism in PCC in AD (Hirono *et al.*, 1998). Thus, there is a tight link between dPCC damage in AD and alterations in visuospatial and visuoconstructive abilities. Evidence for the general contribution of dPCC to visuoconstructional deficits is not limited to damage in MCI and AD. Indeed, strokes in this region also produce spatial disorientation and possibly executive functions that depend on visuospatial coordination as reported in some cases of MCI as discussed in Chapter 13. Thus, damage to dPCC is associated with spatial disorientation and constructional deficits regardless of the source of damage and this includes the deposition of neurofibrillary degeneration in dPCC and their subsequent death.

Circuitry studies of dPCC suggest a coordinated substrate in which functional disorganization between pMCC and dPCC can lead to constructional deficits. A rich body of experimental monkey studies and basal glucose metabolism correlations in human show there are heavy interconnections between dPCC and the sulcal cingulate cortex that contains the caudal cingulate premotor area (cCPMA, reviewed in Chapters 5 and 13). One of the primary functions of dPCC is orientation of the head, limbs and body in space, and the dense projections of this subregion into the cCPMA provides a mechanism for guiding complex movements such as those required for drawing figures and moving to goals in visual space. Moreover, it has recently been suggested that this region is involved in intentions and one's consequent actions (den Ouden *et al.*, 2005) further supporting the role of this region in complex, premotor planning. Thus, damage to dPCC and often pMCC in stroke, AD, dementia with Lewy Bodies and Parkinson's disease with dementia (see Chapter 32) leads to deafferentation of the cCPMA and in some diseases overt neuronal damage thereto. In the present dysexecutive MCI case, there was profound damage to layer V neurons that are frequently involved in motor functions via their projections to the caudate and pontine nuclei and the spinal cord and corticobulbar projections. Highly selective, neuropsychological tests are needed that will herald the earliest neuronal damage to dPCC and its underlying circuits. Eventually, the pMCC and dPCC may become one of the primary sites of diagnostic and therapeutic interventions in neurodegenerative diseases.

The focus of early degenerative events in cingulate cortex in dementia provides not only new impetus to understand its structural and functional organization but also provides new impetus for early detection of damage to this region with higher resolution neuropsychological tests. Early detection is critical because therapeutic interventions will most likely have maximal effectiveness early in the disease process. It is clear that differential diagnosis will be even more important as MCI stages of different diseases are identified in addition to the plethora of subgroups, variants, and subtypes of AD.

Acknowledgments

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